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**Design of three-dimensional engineered protein hydrogels for tailored control of neurite growth.**

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**Public Summary:**

The design of bioactive materials allows tailored studies probing cell-biomaterial interactions, however, relatively few studies have examined the effects of ligand density and material stiffness on neurite growth in three-dimensions. Elastin-like proteins (ELPs) have been designed with modular bioactive and structural regions to enable the systematic characterization of design parameters within three-dimensional (3-D) materials. To promote neurite out-growth and better understand the effects of common biomaterial design parameters on neuronal cultures we here focused on the cell-adhesive ligand density and hydrogel stiffness as design variables for ELP hydrogels.

**Scientific Abstract:**

The design of bioactive materials allows tailored studies probing cell-biomaterial interactions, however, relatively few studies have examined the effects of ligand density and material stiffness on neurite growth in three-dimensions. Elastin-like proteins (ELPs) have been designed with modular bioactive and structural regions to enable the systematic characterization of design parameters within three-dimensional (3-D) materials. To promote neurite out-growth and better understand the effects of common biomaterial design parameters on neuronal cultures we here focused on the cell-adhesive ligand density and hydrogel stiffness as design variables for ELP hydrogels. With the inherent design freedom of engineered proteins these 3-D ELP hydrogels enabled decoupled investigations into the effects of biomechanics and biochemistry on neurite out-growth from dorsal root ganglia. Increasing the cell-adhesive RGD ligand density from 0 to  $1.9 \times 10^7$  ligands  $\mu\text{m}^{-2}$  led to a significant increase in the rate, length, and density of neurite out-growth, as quantified by a high throughput algorithm developed for dense neurite analysis. An approximately two-fold improvement in total neurite out-growth was observed in materials with the higher ligand density at all time points up to 7 days. ELP hydrogels with initial elastic moduli of 0.5, 1.5, or 2.1 kPa and identical RGD ligand densities revealed that the most compliant materials led to the greatest out-growth, with some neurites extending over 1800  $\mu\text{m}$  by day 7. Given the ability of ELP hydrogels to efficiently promote neurite out-growth within defined and tunable 3-D microenvironments these materials may be useful in developing therapeutic nerve guides and the further study of basic neuron-biomaterial interactions.

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